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MAJ HARTWICH SCOTT A

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LIVING ON OKINAWA, JAPAN?

By

SCOTT A. HARTWICH, B.S., M.D.

THESIS

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DEDICATION

To ████████████████ the 2 greatest joys in my life.

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JAPANESE ENCEPHALITIS VACCINE COST-BENEFIT ANALYSIS: IS THE PAIN WORTH THE GAIN FOR U.S. ARMED FORCES ACTIVE DUTY DEPENDENTS LIVING ON OKINAWA, JAPAN?

Scott A. Hartwich, B.S., M.D., M.P.H.
The University of Texas
Health Science Center at Houston
School of Public Health, 2002

Supervising Professor: Alfonso H. Holguin

Japanese encephalitis (JE) is an arboviral disease of major public health importance in Asia, causing approximately 40,000 clinical cases each year. JE infection leads to a viral encephalitis in approximately 1 in 200 infections. Fatalities approach 25% and residual neurologic sequelae in 30% of cases. Drug treatment does not exist, thus vector control and immunization are currently used as main control measures. The specific aim of this thesis is to determine the cost to administer Japanese encephalitis vaccine to all active duty dependents on Okinawa, Japan and evaluate if such a program is economically beneficial given a low risk of clinical cases in the affected population. This analysis was performed from the perspective of the Department of Defense (DoD) Military Treatment Facility (MTF) system on Okinawa. The primary outcome measured was based on treatment costs saved in the prevention of clinical JE infections. The expected overall cost of immunizing 20,945 dependents of AD military members on Okinawa is $2,878,327. Starting an immunization program for all dependents would be expected to prevent 2.9 cases of clinical JE in one year.

The results are based on a conservative estimate of 1.5/10,000 clinical cases per year and a vaccine efficacy of 0.91. Over 3 years approximately 8.7 cases of JE will be prevented. The cost effectiveness ratio per case of clinical JE prevented is $330,842/case. The estimated cost for the acute treatment of one case of clinical JE is $12,493. The overall benefit of preventing 8.7 cases is $108,689. The net benefit and benefit-cost ratio for the program is ($2,769,638) and 0.04 respectively. At the current cost of JE-VAX, according to the Federal Supply Schedule, the incidence of JE must be greater than 40/10,000 persons to become cost-beneficial. A universal JE vaccination program for AD dependents on Okinawa, Japan is not cost-beneficial from the perspective of the Okinawa MTF's. This study is a preliminary look at the economic cost of immunizing approximately 20,945 persons and does not take a societal view for cost basis.

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INTRODUCTION

Japanese encephalitis (JE) is an arboviral disease of major public health importance in Asia, causing approximately 40,000 clinical cases each year. JE infection leads to a viral encephalitis in approximately 1 in 200 infections.[1] Incidence rates of clinical infection range from 1 to 10 per 10,000 persons in areas where JE is endemic.[2] Fatalities approach 25% and residual neurologic sequelae in 30% of cases.[1] Culex mosquitoes, primarily *Culex tritaeniorhynchus*, transmit the virus from viremic animals, mostly domesticated pigs and Ardeid birds (Herons/Egrets), to humans in a seasonal pattern.[3, 4] Drug treatment does not exist, and thus vector control and immunization are currently used as main control measures.

Japanese encephalitis may result in a febrile illness with neurological symptoms ranging from headache to meningitis or encephalitis. Symptoms can include: headache, fever, meningeal signs, stupor, disorientation, coma, tremors, seizures, paresis, hypertonia, and loss of coordination. The encephalitis cannot be clinically distinguished from other central nervous system infections. Etiological diagnosis of JE is mainly based on serological testing, using IgM-capture ELISA, which detects specific IgM in CSF or in the blood of almost patients within 4-7 days of onset of disease.[5]

Current Centers for Disease Control and Prevention Recommendations of the Advisory Committee on Immunization Practices (CDC ACIP) suggest JE vaccination for persons residing in an endemic or epidemic area for 30 or more days during transmission season.[1] The National Advisory Committee on Immunization (NACI) of Canada follows the same recommendations.[6] The Armed Forces Epidemiological Board (AFEB) "recommends

that all personnel and dependents assigned to Okinawa and other enzootic areas be provided

information on Japanese encephalitis (JE), including risk factors and personal protective

measures. All personnel and dependents should be offered vaccine." "Decisions to vaccinate

should not be based solely on geographic locations and ecological considerations in a

relatively geographically-confined area such as Okinawa. Everyone assigned to Okinawa is

at some level of risk."[7]

Okinawa, Japan is considered an endemic region for JE with a transmission season

from April to October. Vector control and aggressive vaccination have resulted in no recent

infections of the local population. Although only 4 cases of clinical JE have occurred on

Okinawa since 1974 (1 Okinawan 1980 and 3 US Marines 1991), the potential exists for an

outbreak among unimmunized persons.[8, 9] Of importance, is the large numbers of U.S.

persons living on the island due to a large military presence and thus are potential candidates

for JE vaccination. Approximate U.S. population numbers are 31,000 active duty military

members and 20,000 dependents at any given time.

The current vaccine approved for use in the U.S. is a mouse brain-derived inactivated

monovalent vaccine produced from the "Nakayama-NIH" strain of JE. Current regimens

used in the U.S. include a 3 dose series for children >1 and adults.[10] AFEB recommends a

booster after 3 years if there is continued exposure.[11] Adverse reactions to the vaccine range

from mild local swelling and pain, to urticaria and angioedema, neurologic sequelae,

anaphylactic shock, and death.

The specific aim of this thesis is to determine the cost to administer Japanese

encephalitis vaccine to all active duty dependents on Okinawa, Japan and evaluate if such a

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program is economically beneficial given a low risk of clinical cases in the affected population. This analysis will be performed from the perspective of the Department of Defense (DoD) Military Treatment Facility (MTF) system on Okinawa. The primary outcome measured will be based on treatment costs saved in the prevention of clinical JE infections.

BACKGROUND

JAPANESE ENCEPHALITIS VIRUS VACCINE INACTIVATED (JE-VAX)

The JE vaccine (JE-VAX) has been licensed for use in the U.S. since 10 Dec 1992 mainly for U.S. military use and overseas travelers. It is an inactivated vaccine derived from infected mouse brain and manufactured by the Research Foundation for Microbial Diseases of Osaka University (BIKEN). Formaldehyde is used to inactivate the Nakayama-NIH strain virus, gelatin added as a stabilizer, and thimerosal is used as a preservative.[1] The BIKEN vaccine has been licensed in Japan since 1954, and is the most widely used immunization for JE on a worldwide basis[12] Vaccine efficacy was demonstrated in a placebo-controlled randomized clinical trial in Thai children between the ages of 1 and 14. The observed efficacy was 91% (95% confidence interval 54% to 98 %) for the BIKEN vaccine.[13]

Local reactions

Adverse reactions to the BIKEN vaccine are common, and also varied. Local reactions including tenderness, swelling, and redness occur about 20% of the time.[14, 15] In 1990 a US Army study, using 538 adult volunteers, found local soreness and redness in 21% of vaccinees after the first dose. Subsequent doses noted a decreased local effect. Less than 1% of all reported symptoms were graded as severe, and no urticaria or angioedema was noted.[16]

General systemic effects

General systemic side effects including fever, headache, malaise, rash, GI symptoms, and myalgia, occur approximately 10% of the time.[14, 15] The 1990 US Army study noted headaches in 15.2% of vaccinees, and febrile episodes in 5.2% of vaccinees.[16] A CDC study (1983-87) of 1756 U.S. travelers noted less than 5% of vaccinees reported headaches, flu-like symptoms, or fever. Hives were reported in 0.2% of vaccinees, and facial swelling in 0.1% of vaccinees.[14] Both studies were conducted using a 3 dose regimen.

Systemic allergic reactions

Systemic allergic reactions have been noted in the literature since 1989. Events include urticaria, angioedema, respiratory distress, and circulatory collapse. Although most reactions were usually treated with antihistamines and oral steroids, some cases required hospitalization and specialized care. The highest number of adverse reactions to JE vaccine has been reported in Denmark. Denmark reported 150,000 doses distributed and 62 cases

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with allergic mucocutaneous reactions from 1989-1993. Ten persons were hospitalized. Subsequent case control studies have noted that persons developing allergic reactions after immunization were more likely to have a previous history of urticaria, rhinitis, or other allergy.[17] Prior to 1995, Japan reported no occurrence of systemic allergic reactions.[18] The Japanese National Adverse Reactions Reporting System (NARRS) has had 14 cases of anaphylactic shock and 25 cases of anaphylactic reactions reported from April 1996 to March 1998. The Ministry of Health and Welfare has calculated a rate per million doses of 1.9 for anaphylactic shock, and 3.4 for anaphylactoid reactions.[19] Since 1994, two deaths from anaphylaxis have occurred in South Korea.[20] The United States distributed 717,000 doses of JE-VAX between 1993 and 1997. The national Vaccine Adverse Events Reporting System (VAERS) has had 31 reports of urticaria and/or angioedema, for a rate of 1/22,500 doses. No cases of anaphylactic shock were reported during the above time period. Six persons were hospitalized. Also one 6 year old male, whose symptoms started 13 days after immunization, died with brain edema and pneumonia present.[19]

A large scale US Navy prospective study immunized 35,253 persons (US military and dependents) from November 1991 to May 1992 using the BIKEN vaccine. The overall adverse reaction rate was 62.4 per 10,000 vaccinees. Adverse reactions to the vaccine included pruritis, angioedema, urticaria, and dyspnea. Nine persons were hospitalized (2.6 per 10,000 vaccinees) with non life-threatening adverse reactions. One person (21 year old active duty member) died 60 hours after receiving the first dose of the JE vaccine. Confounding factors include a history of recurrent hypersensitivity, a previous episode of anaphylaxis, and receiving a third dose of plague vaccine 12 to 15 hours prior to death.[21]

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Several case control studies have demonstrated an association between allergic reactions to JE vaccine, and a previous history of allergic reactions to other triggers. A U.S. Navy study reported an association between allergic reactions to JE vaccine and a past history of urticaria (triggered by hymenoptera envenomations, medications, physical or other provocations, or an idiopathic cause), allergic rhinitis, or any other allergy.[21] An Australian study described a possible association between receiving another immunization in the previous two weeks, increased alcohol consumption, and a history of contact with dogs.[22] Finally, a Danish study reports the main risk factors for an allergic reaction to the JE vaccine include young age, female gender, and a previous allergic reaction of any kind.[17]

Neurologic adverse reactions

Neurologic adverse events (primary encephalitis, encephalopathy, seizures, and peripheral neuropathy) have been documented in the literature as a result of immunization with the BIKEN vaccine. Japan reported a rate of 1 to 2.3 per million vaccinees from 1965 to 1973.[1] Two cases of severe neurologic illness were reported between 1987 and 1989 (1 case of transverse myelitis and 1 complicated case including seizure, cerebellar ataxia, cranial nerve paresis, and behavioral disorder). Seven cases of acute disseminated encephalomyelitis were reported from 1992 to 1995.[23] From April 1996 to March 1998, NARRS reported 13 cases of irreversible neurologic disorders for a rate of 1.8 per million doses.[19] Between 1982 and 1995, Denmark distributed 350,000 doses of vaccine resulting in 3 cases of acute disseminated encephalomyelitis. South Korea reported 4 cases of severe neurologic illness in 1994. Two children died, 1 child had mental retardation, and 1 child

recovered. Two cases resulted in a diagnosis of encephalopathy and acute disseminated encephalomyelitis. A formal reporting system was initiated in 1995 and has resulted in 1 case report of death in 1996 resulting from severe neurologic dysfunction.[20] One case of Bell's palsy has been reported from Thailand.[10]

ECONOMIC EVALUATION OF VACCINE PROGRAMS

Economic evaluation of healthcare interventions has developed into a modern part of health care decision making. Rising costs, scarcity of resources, and spending limits have developed a need to evaluate healthcare in terms of economic efficiency. The economics mode of thinking is based on scarce resources, and the idea that choices must be made on how to share the available resources. Economic efficiency results when resources are being used in a way that maximizes the benefits obtained from the use of those resources.[24]

The prophylactic use of vaccines has inherently brought about the discussion of benefits, risks, and costs associated with their use. The basic aim of vaccination is to prevent more of the severe complications of the respective disease than might be caused by the vaccine itself.[25] Patients and their physicians evaluate the need and use of vaccines, based on individual scenarios. Economists and policy analysts attempt to evaluate vaccines for the population as a whole, or for certain groups in a population.[26] The overall success of an immunization program depends upon public acceptance that the individual and collective benefits of immunization outweigh the risks.[27]

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Types of economic evaluation

Economic evaluations of vaccines have been broken down into 2 main techniques, cost-benefit and cost-effectiveness analysis.[26] Cost-benefit analysis involves measuring costs and benefits in identical units, usually monetary. The use of this technique addresses the question of whether the benefits of a vaccine are greater than its costs. Since all units being valued are identical, comparison between different interventions can be made using net benefits ratios. Cost-effectiveness analysis measures health benefits in natural units, such as life years saved or illness days saved. The major question this technique addresses is whether one intervention is more cost efficient than another. A major limitation of this technique is its inability to compare interventions with differing natural units.[28]

Perspectives of economic evaluation

The viewpoint chosen for the economic evaluation is very important in determining what costs are included in the analysis, and the types of outcomes measured. Examples of different viewpoints include individuals, institutions, third party payers, a given population, and society. Health economists generally advocate adopting a societal viewpoint whenever possible.[29] The societal viewpoint includes the impact of an intervention on the welfare of society, as a whole. The main reasons this viewpoint is used are study comparability, and the facilitation of policies that maximize the welfare gains of society.[30] Broad viewpoints are most relevant to those concerned about the overall allocation of health resources.[31] Narrow viewpoints are acceptable if explicitly identified, and the needs of potential decision makers (government, purchaser, provider, etc.) are met by the research question posed.[29]

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Costs

Costs for a vaccination program can be divided into direct and indirect costs. Direct costs include the cost of the vaccine, operational costs (supplies, buildings, labor), and the cost of treating vaccine complications. Indirect costs can include values of lost worker productivity, patient insurance co-payments, and out of pocket expenses (transportation, childcare, etc). Prices of resources used can be obtained from finance departments of institutions, or from national statistics.[26]

Immunization costs for dependent civilians are covered by the local MTF's operating budget. Besides actual vaccine cost, the MTF is responsible for personnel, ancillary supplies, and other incidentals. Unfortunately except for specific vaccines or immunization programs, such as Anthrax vaccine and Tick-borne encephalitis vaccine, total accounting for personnel and ancillary costs for immunization implementation is not possible in the current DoD system.[14]

MTF treatment costs can be calculated using DoD third party reimbursement rates. Although dependents of active duty service members are not personally responsible for payments to the MTF, any other insurance coverage in force is billed for treatment costs. The formula for inpatient reimbursement is based on the cost per appropriate diagnosis related group (DRG), and the inpatient adjusted standardized amount (ASA) factor for the appropriate MTF. The cost per DRG is based on the inpatient rate per hospital discharge, weighted to reflect the intensity of the principal and secondary diagnosis, surgical procedures and patient demographics. The value of the inpatient DRG cost is made up of 96% hospital costs and 4% professional charges. The process for determining ASA factors for MTF's is

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comparable to procedures used by the Health Care Financing Administration (HCFA) to determine direct care expenses associated with direct patient care. Outpatient visits are reimbursed on a per clinic visit, based on the appropriate clinical service providing care. The value of outpatient cost per visit is made up of 89% outpatient service costs and 11% professional charges.[32, 33]

Benefits

Benefits of a vaccination program include a reduction in morbidity and mortality from the prevention of a given disease.[26] Such benefits include savings in treatment costs of the given disease, savings from the prevention of mortality, savings from the prevention of long term sequelae, and savings from lost productivity. Primary outcome measures should be clearly stated and benefits determined from the viewpoint of the economic evaluation.[29] Depending on the analysis performed, the units reported are determined. Cost-benefit analysis reports benefits in monetary terms. Cost-effectiveness analysis reports benefits in physical units such as life years gained and cases avoided. In a cost-utility analysis, a variant of the cost-effectiveness analysis, the outcome is healthy years. Different benefits are weighted to produce a composite index value such as quality-adjusted life year.[31]

Method for risk-benefit and cost-benefit analysis of vaccines

Wiedermann and Ambrosch in 1979 presented a paper on the formulas for the calculation of the risk-benefit ratio (Q), risk-benefit difference (D), cost-benefit ratio (Qc), and cost-benefit difference (Dc) for vaccinations. The formulas were developed in an effort

to obtain an objective and dispassionate analysis of a vaccination procedure from a medical and socio-economic point of view.[25]

The risk-benefit ratio expresses how many times mortality, or complications of the disease in question, can be expected more frequently in an unvaccinated population versus a vaccinated population. The risk connected with the disease is weighed against the risk connected with the vaccine, plus vaccination failures. Major risks of vaccination such as death, encephalopathy, and paralysis should be considered. A vaccination is beneficial if $Q>1.0$. Occasionally a very small risk of disease, with at least some risk of vaccination, will render Q near zero and subsequently persuade one to not recommend continued vaccination. Smallpox vaccination is one example where the risk of disease is extremely small and risks associated with vaccination are present.

The risk-benefit difference expresses the yearly number of deaths or ailments prevented by the vaccine, minus the number of deaths or ailments induced by the vaccine per year. If $D>0$ then the vaccine is considered beneficial from a social economic point of view.

The cost-benefit ratio (Qc) expresses how many times treatment of a disease is more expensive than vaccination. Expected costs of disease treatment are weighed against costs of vaccination. A vaccination is considered profitable if $Qc>1.0$.

The cost-benefit difference (Dc) expresses the amount of money saved by a vaccination procedure. A vaccination is considered profitable if $Dc>0$.

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MATERIALS AND METHODS

Purpose: To determine the cost of administering Japanese encephalitis vaccine to all active duty dependents on Okinawa, Japan and evaluate if such a program is economically beneficial given a low risk of clinical cases in the affected population. This analysis is performed from the perspective of the DoD MTF system on Okinawa. The primary outcome measured is based on treatment costs saved in the prevention of clinical JE infections. Although mortality and long-term neurologic disability are complications, the benefits of being prevented are not used in this analysis. Such benefits are societal in form and do not directly affect the JE immunization program from DoD's Okinawa MTF system perspective.

STUDY DESIGN

Risk-benefit and cost-benefit analysis of JE-VAX using the below formulas (Appendix A).[25]

Risk-benefit ratio (Q) was determined by the following formula:

$Q = Rt/[r + (1-p) Rt]$

Rt=risk of disease over time period t

r=risk of vaccination adverse reaction

p=protection rate

(1-p)Rt=risk of vaccination failures over time period t

Risk-benefit difference (D) was determined by the following formula:

$D = pR - (r/t)$

R=risk of disease

p=protection rate

(r/t)=risk of major adverse reaction from vaccine

t=time period of protection

Cost-benefit ratio (Qc) was determined by the following formula:

$Qc=Cth/Cv$

Cth=expected overall costs of therapy avoided by vaccination

Cv=expected overall cost of vaccine

Cost-benefit difference (Dc) was determined by the following formula:

$Dc=Cth-Cv$

Cth=cost of therapy avoided by vaccination

Cv=overall cost of vaccine

VARIABLES

Total cost of vaccination

The total cost of vaccination (Cv) is equal to the cost of the vaccine for the defined population, plus the cost of treatment for potential vaccine related adverse reactions. Vaccine unit cost was based on the current DoD cost in acquiring the single 3 dose unit package of JE-VAX manufactured by Aventis Pasteur. The vaccine cost basis is $136.20 according to the Federal Supply Schedule.[34] Also for comparison the Red Book 2001 cost basis was used in the analysis. The 2001 Red Book cost for the same 3 single dose package is $293.63.[35] Assumptions were made in regards to starting a universal vaccination program for the targeted population. I assumed that each person received the 3 dose series. No wastage of vaccine occurred due to the use of the 3 single dose unit package. The estimated population numbers are based on Tricare April 2002 enrollment data for the Okinawa MTF's. Other operational costs (supplies, office, and personnel charges) were not taken into account. These operational costs are already paid for as the new program will be incorporated into the present immunization programs run by MTF's on Okinawa.

Costs due to complications of the vaccine were only used for conditions requiring hospitalization (anaphylaxis, neurologic events, severe urticaria, and angioedema). Risk of vaccine per dose administered (r) was based on published results involving US citizens living on Okinawa. A large scale US Navy prospective study immunized 35,253 persons (U.S. military members and dependents) from November 1991 to May 1992 using the BIKEN vaccine. A vaccine risk rate of 2.6/10,000 persons requiring hospitalization was

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documented.[21] The cost of treatment was calculated using the FY 2002 Department of Defense (DoD) reimbursement rates. This formula is based on the cost per appropriate diagnosis related group (DRG- last updated in FY 2000), and the inpatient adjusted standardized amount (ASA) for admission to Camp Lester Naval Hospital, Okinawa.[32, 33] The DRG used (allergic reaction diagnosis) was based on the above study's lack of encountering neurologic adverse effects after vaccination (Appendix B). The calculated cost would normally be billed to dependent's insurance company if they are insured. An assumption was made that this is the actual cost borne by DoD for the treatment of each JE-VAX adverse reaction requiring hospitalization. Minor complications are not included.

Cost of therapy to treat clinical JE

Risk of clinical Japanese encephalitis (Rt) was estimated over a 3 year period. The yearly incidence rate of 1.5/10,000 persons is based on published results reviewed by T.F. Tsai. The calculated rate is the last published incidence rate data from Okinawa, Japan. The incidence rate was calculated using a susceptible and unimmunized population of U.S. Marine Corps members.[19] It is assumed that the population being immunized has not been previously exposed to JE. Previous studies in Taiwan (1965) and Thailand (1984-5) have noted an annual rate of 1.8-2.5/10,000 persons in placebo trials and unvaccinated populations.[19]

The cost of therapy (Cth) was calculated using the same treatment cost formula noted above, and using the appropriate DRG group (other infectious and parasitic disease diagnosis). Costs were determined using published FY 2002 DoD reimbursement rates for

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inpatient services based on the appropriate DRG, and care provided at Camp Lester Naval

Hospital, Okinawa (Appendix B). No long-term rehab costs were computed as generally

these costs will be borne by other payers (Medicare, private insurance, Medicaid, etc), not

DoD. Also any patient requiring long-term disability care would be transferred to the U.S.,

as Lester Naval Hospital does not have long-term care facilities. The cost of hospitalization

per clinical case was determined, and multiplied by, the expected number of clinical cases

avoided over the 3 year period before revaccination is currently recommended. The

protection rate is 91% for the BIKEN vaccine.[13] The subsequent value obtained is the overall

benefit of the immunization program.

Sensitivity analysis

Sensitivity analysis was performed on incidence rates and vaccine unit cost.

Incidence rates and vaccine cost are the main factors affecting the decision to institute a

vaccine program. The incidence rate was increased, and vaccine costs decreased, to evaluate

how these 2 factors affect the benefit-cost ratio.

POPULATION

U.S. military active duty dependent population estimated on Okinawa by Tricare

April 2002 enrollment data. The estimated population is 20,945 persons (Appendix C). The

population will be assumed to obtain 3 doses of the vaccine. Most persons serve a 3 year

tour of duty and will depart before needing a booster dose after 3 years. Unless increases or

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decreases in active duty troop strength occur, it is reasonable to assume that the average

population on Okinawa will not drastically change over time.

RESULTS

The unit cost of JE-VAX for a 3 dose series is based on the current 3 single dose vial

package manufactured by Aventis Pasteur. The unit cost based on the current Federal Supply

Schedule is $136.20. The unit cost based on the 2001 Red Book is $293.63. The vaccine cost

of immunizing 20,945 dependents of AD military members on Okinawa, based on the

Federal Supply Schedule, is $2,852,709. While the vaccine cost, based on the 2001 Red

Book, is $6,150,080. The estimated cost to treat 1 hospitalization due to an adverse reaction

to JE-VAX is $12,493 (Appendix B). The expected number of hospitalizations due to

adverse reactions to the vaccine is 5.4 cases with a total cost of $25,618. The overall cost of

the vaccination program is $2,878,327 based on the government supply schedule and

$6,175,698 based on Red Book values respectively (Table 1). Resulting overall costs are

based on a program designed to immunize 100% of the 20,945 AD dependent population on

Okinawa.

A total of 3.1 clinical cases of Japanese encephalitis would be estimated to occur

without an immunization program in one year. Starting an immunization program for all

dependents would be expected to prevent 2.9 cases of clinical Japanese encephalitis in one

year. These results are based on a conservative estimate of 1.5/10,000 clinical cases per year,

and a vaccine efficacy of 0.91. This estimate is based on previous reported incidence rates in

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an unimmunized population on Okinawa and rural Taiwan. Over 3 years, approximately 8.7 cases of JE will be prevented. The cost effectiveness ratio per case of clinical JE prevented, based on the Federal Supply Schedule, is $330,842/case. The cost effectiveness ratio based on the 2001 Red Book cost is $709,850 per JE case prevented (Table 1).

The estimated cost for the acute treatment of one case of clinical JE is $12,493 (Appendix B). The overall benefit of preventing 8.7 cases is $108,689. The net benefit and benefit-cost ratio for the program based on the Federal Supply Schedule is ($2,769,638) and 0.04 respectively. The 2001 Red Book associated values are ($6,067,009) and 0.02 (Table 1). Based on these values, there is no benefit of undertaking the defined immunization program. A benefit-cost ratio is considered beneficial if it is >1.0. From the point of view of the MTF's on Okinawa, the money needed to fund this program may be better spent on other projects.

Table 1: Estimation of costs and benefits of JE immunization program

Category	Federal Supply Schedule	Red Book
Cost		
Unit cost -3 single dose package	$136.20	$293.63
Total immunization cost	$2,852,709	$6,150,080
Adverse reaction cost	$25,618	$25,618
Overall Cost of program	$2,878,327	$6,175,698
Effectiveness (case prevented)		
Cases prevented in 1 year	2.9	2.9
Cases prevented in 3 years	8.7	8.7
Cost/effectiveness ratio	$330,842/case	$709,850/case
Benefit from 1 prevented case		
Savings in treatment cost	$12,493	$12,493
Overall benefit of program	$108,689	$108,689
Net benefit of program	($2,769,638)	($6,067,009)
Benefit/cost ratio	0.04	0.02

The benefit-risk ratio (Q) was calculated as 1.5. The benefit-risk difference (D) was calculated as 4.98E-5 and can be found in table 2. Both values are interesting in that they support the idea that JE-VAX is beneficial based on the risk of JE, the risk of adverse effects due to the vaccine, and the protection rate of the vaccine. The benefit-risk ratio (Q) weighs the risk of disease against the risk of vaccination plus vaccination failures. If Q>1 the vaccine is beneficial. The benefit-risk difference (D) looks at the difference between cases of disease prevented by a vaccine and adverse effects induced by it. If D>0 then the vaccine can be considered beneficial.

Table 2: Calculated ratios and differences for the JE immunization program based on the 3 single dose cost package

Category	Federal Supply Schedule	Red Book
Benefit-risk ratio(Q)	1.50	1.50
Benefit-risk difference (D)	4.98E-5	4.98E-5
Benefit-cost ratio (Qc)	0.04	0.02
Benefit-cost difference (Dc)	($2,769,638)	($6,067,009)

Table 3 presents the benefit-cost ratio of the proposed JE immunization program for AD dependents on Okinawa. At the current cost of JE-VAX, according to the Federal Supply Schedule, the incidence of JE must be greater than 40/10,000 persons to become cost-beneficial. Such an incidence would be quite unlikely and was last seen in US soldiers in Vietnam during 1972. A report was published in which 9 cases were identified in a population of 2,101 soldiers. The calculated incidence rate was 42.8/10,000 soldiers.[19] Lowering the vaccine cost to $34, for all 3 doses, would decrease the necessary incidence rate to approximately 10/10,000 persons to become cost-beneficial. Again, this is a highly unlikely event.

Table 3: Sensitivity analysis of the benefit-cost ratio for JE vaccination program by varying the JE incidence rate and the 3 single dose Federal Supply Schedule vaccine cost

JE incidence	Vaccine Cost				
	$136.2	**$102.15**	**$68.10**	**$50**	**$34**
1.5/10,000	0.04	0.05	0.07	0.10	0.15
10/10,000	0.25	0.33	0.49	0.67	0.97
20/10,000	0.50	0.66	0.98	1.33	1.94
30/10,000	0.66	0.88	1.31	1.77	2.58
40/10,000	0.99	1.32	1.97	2.66	3.87
50/10,000	1.24	1.65	2.46	3.33	4.84

DISCUSSION

JE is a potential problem for all AD dependents living on Okinawa during the transmission season of April to October. Japan has an extensive program including immunization, vector control, vector trapping, and sentinel yearling pig surveillance which has lowered the annual number of cases to less than 10 nationwide. The incidence of 1.5 cases per 10,000 persons was used for the cost-benefit analysis because it was the last published rate for non-immunized persons on Okinawa. The conservative rate is similar to the incidence of 2.5 and 1.8 per 10,000 persons found in studies in Taiwan for placebo recipients (vaccine trial) and unvaccinated persons.[19]

The cost-benefit analysis performed from the point of view of the Okinawa MTF's suggests that universal vaccination of all AD dependents is not cost-beneficial. Based on the current cost of the vaccine, and low incidence of JE, immunizing all AD dependents on Okinawa would be extremely expensive, and the potential number of persons hospitalized with adverse reactions is high. Even lowering the cost of the vaccine to $34 for the series would not be cost-beneficial until the incidence of disease is increased to above 10 per 10,000 persons. Both situations are highly unlikely. This economic analysis has some limitations that will be discussed further. It should also be pointed out that the limited view of this analysis pertains only to the populations identified. Limitations include a very specific perspective, costs which do not include future earnings lost or chronic care, and the inability to value non-monetary benefits.

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The analysis was performed from a very specific perspective. Only the costs and benefits incurred by Okinawa MTF's are used for the analysis. This perspective allows one to evaluate the program based on limited funds available to the MTF's. Each MTF has a yearly budget that must be dispersed throughout all medical care areas. The addition of a program involves either requesting a larger budget, or reallocating monies from other areas. This perspective analyzes all benefits and costs no matter who receives them. An important part of this analysis is opportunity cost and its effect on resources not available to society. Opportunity cost includes lost productivity.[36] A societal approach facilitates maximizing welfare gains or minimizing losses to society. Most cost-benefit analyses take a societal perspective to compare results throughout the healthcare system.[30] Although the presented analysis is narrow, this approach allows for an efficient analysis of a highly specific program. It takes into account only the costs inherited by MTF's on Okinawa. Limited healthcare resources can thus be allocated in the most beneficial way possible.

The cost of chronic care and death were not used in this analysis due to the limited perspective used. Chronic care would take place off Okinawa as the U.S. Naval hospital does not participate in long term care. Ultimately, another payer would assume the cost of care and it would not come out of the Okinawa MTF's budget. Death benefits are not paid by the DoD for dependents. Also future earnings lost do not affect the MTF's budget.

An interesting area not analyzed but important in determining whether a program is beneficial, or not, is the valuation of costs and benefits that have indirect monetary values. Some areas that should be evaluated include potential for pain and suffering, psychological stress, political fallout, community fear of disease, loss of community morale if a case of JE

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appears, and decreased performance by the active duty member. It is difficult to value these costs, but these indirect costs can make it beneficial to start, or continue, an otherwise non cost-beneficial program. Prevention-effectiveness studies are only tools in the decision making process. They do not make the decisions themselves.[36]

The multifaceted JE eradication program in Japan, and specifically on Okinawa, has reduced the risks of inhabitants becoming infected with JE. Unfortunately how much each individual part of the overall program contributes to the reduction in cases is unknown. Vector control and urbanization are important parts of the overall control process but are difficult to measure. Diminished land area for rice cultivation and the use of pesticides has reduced vector populations. Urbanization, and changing the process of pig farming, has led to physical separation of humans and the principal viral amplifying host. The urbanization of Singapore has been associated with an interruption of the JE virus transmission. A serosurvey indicates no JE immunity in children less than 12 years of age.[19] Mosquito trapping on Okinawa between 1988 and 1993 has shown a decrease in the abundance of the JE vector. But, where the vector was most prevalent was linked epidemiologically to the 3 cases involving US Marines in 1991. The trapping pattern suggests the presence of a gradient of risk between the test sites surveyed.[3] This data suggests that the risk of exposure is geographically based on Okinawa, and that urban and suburban residents are at a low risk of exposure to the vector necessary for infection.

Further studies need to be developed to identify the current incidence of JE in unimmunized persons in Okinawa and other closely related geographic and economic regions such as Taiwan. Current data is from 1965 for Taiwan and 1991 for Okinawa.[19] Serosurveys

can be used to determine previous infections in unimmunized persons. Another area that needs to be continually updated is the prevalence of vectors and the virus in virus amplifying hosts. A study designed to predict outbreaks by location may make it possible to identify persons who would be at increased risk of JE. This would allow focused immunization, reducing the number of persons at a relatively low risk from suffering adverse effects during JE vaccination. Another important study that should be performed is a cost-benefit analysis of JE vaccination in US persons traveling overseas to JE endemic areas. An economic analysis using a societal perspective would add more evidence for whether or not Public Health officials should recommend the vaccination to the international traveler.

Economic analysis of vaccination programs has important implications in the future of Public Health. The current interest in biologic weapons and the potential for the introduction of lethal microorganisms into immunological naïve populations has opened up Pandora's box. Society is being asked what it is willing to pay, and what risks it is willing to undertake, to have the risk of a potential illness reduced. Experts are considering what risks are acceptable and how much large programs will cost. Although only a part of the decision process, risk-benefit and cost-benefit analysis are important to the policy makers. We live in a society of limited resources and ultimately any program needs to provide the greatest good, for the most people, at the least possible cost. Well performed economic analysis is a tool to help this vision become a reality.

The ultimate question comes down to what should be done to prevent JE in AD dependents on Okinawa? All persons on Okinawa are at least at some risk to become infected. Persons who camp, hike, bike, or live in rural areas on the island potentially come

into contact with the vector more often than those in urban or suburban areas. Using DEET, long shirts and pants, avoidance of pig farms and rice fields, and staying indoors during the mosquitoes' peak times is common sense that needs to be communicated. Immunization of these selected persons may be appropriate with the intended vaccinee's consent to side effects of the vaccine, and understanding that vaccination is only 1 part of the prevention program. Continued surveillance of the vector and the virus amplifying host is important to predict increased risk of exposure. Also pesticide application as necessary around the island will help to keep the vector under control. One must remember that clinical JE cases can occur in the population of Okinawa as long as the vector, virus, and hosts exist.

CONCLUSIONS

A universal JE vaccination program for AD dependents on Okinawa, Japan is not cost-beneficial from the perspective of the Okinawa MTF's. This study is a preliminary look at the economic cost of immunizing approximately 20,945 persons and does not take a societal view for cost basis. Further studies need to be fielded to obtain current incidence rates of JE for unimmunized persons and identify demographic factors that increase the risk of becoming infected with JE. I would recommend a focused immunization program based on time spent outdoors near the vector's breeding grounds during April to October. An associated education program identifying the risks of being bitten by the vector and how to protect oneself with clothing, DEET, and timing of activities. Continued active surveillance of the vector, and virus amplifying hosts, can help identify increased risk of JE. Also

continued cooperation with Japanese health officials can help facilitate timely information sharing.

The views expressed in this thesis are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.

APPENDICES

Appendix A: Calculations for Ratios and Differences

Risk-benefit ratio (Q) is determined by the following formula:

$Q = Rt/[r + (1-p) Rt]$

Rt=risk of disease over time period t

r=risk of vaccination adverse reaction

p=protection rate

(1-p)Rt=risk of vaccination failures over time period t

Risk-benefit difference (D) is determined by the following formula:

$D = pR - (r/t)$

R=risk of disease

p=protection rate

(r/t)=risk of major adverse reaction from vaccine

t=time period of protection

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Cost-benefit ratio (Qc) is determined by the following formula:

$Q_c = C_{th}/C_v$

C_{th} = expected overall costs of therapy avoided by vaccination

C_v = expected overall cost of vaccine

Cost-benefit difference (Dc) is determined by the following formula:

$D_c = C_{th} - C_v$

C_{th} = cost of therapy avoided by vaccination

Variable	Value
Rt	0.00045
r	0.00026
p	0.91
t	3
Q=Rt/[r + (1-p)Rt]	**1.50**
R	0.00015
p	0.91
r	0.00026
t	3
D=pR - (r/t)	**4.98E-5**
Cth	$108,689
Cv (Federal Supply Schedule)	$2,878,327
Qc=Cth/Cv	**0.04**
Dc=Cth-Cv	**($2,769,638)**

Appendix B: Inpatient hospital rates for 1 case of clinical JE and 1 hospitalized allergic reaction to JE-VAX [33]

Diagnosis	Diagnosis related group (DRG)	DRG Weight (Tricare/ Champus Rate)	MTF adjusted standardized amount (ASA) for Okinawa	Total inpatient cost for 1-29 days of hospitalization
OTHER INFECTIOUS & PARASITIC DISEASE	423	1.2824	$9,742	$12,493
ALLERGIC REACTIONS AGE >17	447	0.487	$9,742	$4,744

Appendix C: AD dependent population per enrolled MTF on Okinawa, Japan[37]

MTF location	Population as of April 2002
Naval Hospital Okinawa	5,232
Kadena	9,525
Futemna	0
Schwab	0
Hansen	0
Kinser	1,919
Bush-Courtney	2,918
Evans-Foster	1,351
Total Population	**20,945**

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VITA

Scott Alan Hartwich was born in Camarillo, CA ██████████ to ██████
████████████████████████. In 1990, he graduated summa cum laude with a

B.S. in biology, and minors in chemistry and business administration, from Albertson

College of Idaho. He attended medical school at the Uniformed Services University of

the Health Sciences in Bethesda, Maryland graduating with an M.D. degree in 1995.

After completing a PGY-1 year in general surgery at Keesler Medical Center, Biloxi, MS,

he attended the Aerospace Medicine Primary course at the United States Air Force

School of Aerospace Medicine. During his next 3 year assignment to Kadena AB,

Okinawa, Japan, he was a hyperbaric treatment physician, squadron medical element

leader, chief of physical exams and standards (PES), occupational health working group

chairman, flight chief, and travel medicine consultant. He deployed to multiple locations

including a 4 month tour as the Combined Task Force clinic chief as part of Operation

Northern Watch. In 1999 he was reassigned to Spangdahlem AB, Germany. While

there, he was chief of PES, occupational medicine consultant, project manager for

instituting the Preventative Health Assessment program, and medical officer on a Class 1

aircraft mishap investigation. In the summer of 2001, he started an M.P.H. program at

the University of Texas Health Science Center at Houston-San Antonio campus as part of

a residency in aerospace medicine (RAM). He is married to ██████████ of New

Jersey and has 1 daughter, ██████████.

This thesis was typed by Scott A. Hartwich, M.D.